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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,662	10/21/2005	Peter John Ratcliffe	06843.0091	4806

22852 7590 04/04/2008

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
04/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,662	RATCLIFFE ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-25 and 27-33* is/are pending in the application.

4a) Of the above claim(s) *7-25,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/15/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 08/09/2007), Applicants filed a response and amendment received on 12/19/2007. Said amendment cancelled Claims 2 and 26; amended Claims 1 and 29.

Claims 1, 3-25 and 27-33 are pending in the instant Office action. Claims 7-25 and 27-28 are withdrawn as being drawn to non-elected inventions.

Thus, Claims 1, 3-6 and 29-33 will be examined herein.

Information Disclosure Statement

2. The missing Information disclosure statements (IDS) filed on 04/15/2005 is included in the instant office action and has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Maintained-Compliance with Sequence Rules

3. The previous non-compliance with Sequence Rules for a structural coordinates in Table 3 (total of four coordinates) is withdrawn by virtue of Applicants' amendment.

4. The previous non-compliance with Sequence Rules for the polypeptide in Figure 3 or 4 is withdrawn by virtue of Applicants' amendment.

Maintained-Compliance with Sequence Rules

5. The previous non-compliance with Sequence Rules for the Table 2 is maintained. Applicants has amended the specification (see page 3, filed on 12/19/2007) and recites "Table 2, Partial sequence alignment of FIH with a selection of JmjC domain containing protein (SEQ Id NOs 4-20, respectively, in order of appearance). However, the Table 2 contains only 17 polypeptides. It is also confusing which is which without description that is more detailed. Appropriate correction is required.

6. The previous non-compliance with Sequence Rules for the polypeptide in page 35, line 16, does not have appropriate SEQ ID NO.

Withdrawn-Objections to the Specification

7. The previous objection of specification because the title is not descriptive of the claims is withdrawn by virtue of Applicants' amendment.

8. The previous objection of specification because it does not recite all SEQ ID NOs filed in the sequence listing is withdrawn by virtue of Applicants' amendment.

Objections to the Specification

9. The specification is objected because the Table 2 has many gray areas wherein amino acid(s) cannot be deciphered. Appropriate correction is required.

Withdrawn-Claim Objections

10. The previous objection of Claim 29 for reciting “co-ordinates” is withdrawn by virtue of Applicants' amendment.

11. The previous objection of Claims 1, 4-6, 29, 32 and 33 for reciting “FIH” or “HIF” is withdrawn by virtue of Applicants' amendment.

12. The previous objection of Claims 1, 4-6, 29, 32 and 33 for the use of abbreviations FIH is not consistent through out the Claims is withdrawn by virtue of Applicants' argument.

Claim Rejections - 35 USC § 112

13. Claims 6 and 33 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection was stated in the previous office action as it applied to previous Claims 6 and 33. In response to this rejection, applicants have cancelled Claims 2 and 26; amended Claims 1 and 29 and traverse the rejection as it applies to the newly amended claims.

Applicants argue that the specification (i.e., asparagine 803 encompasses the asparagine equivalent to Asn 803 of HIF) sufficiently describes the point of reference.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Examiner acknowledge "USPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure" but the "Limitations appearing in the specification but not recited in the claims should not be read into the claim" (see MPEP 2106[R-5] II). Thus, the instant rejection is maintained.

14. Claims 1, 3-6 and 29-33 are rejected under 35 U.S.C. 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous Claims 1, 3-6 and 29-33. In response to this rejection, applicants have cancelled Claims 2 and 26; amended Claims 1 and 29 and traverse the rejection as it applies to the newly amended claims. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue the written description and scope of enablement together and it seems the argument is really focused on the scope of enablement. Applicants merely disagree and traverse the instant rejection because the specification adequately defines the term FIH as "References to FIH herein refer to FIH and homologues thereof" on page 4, line 25 of instant specification. Thus, Applicants provide almost no valid

argument regarding instant rejection based on the lack of correlation between structure and function for claimed genus method so that one skilled in the art would be able to posses the full scope of claimed method. It is unclear how FIH referring to FIH is adequate description of FIH. The recitation of homologues thereof is even broader then FIH according to the recited definition in the specification. Thus, the interpretation of FIH in the previous office action is proper.

As noted previously, instant application describes four structural coordinates of 1H2K, 1H2L, 1H2M and 1H2N (see Table 3) for a method of identifying , screening, characterizing or designing a chemical entity which binds to human Factor Inhibiting Hypoxia Inducible Factor (FIH) identified as Q969Q7 (NCBI database). The recited FIH is not defined by the instant specification; thus, the instant FIH has been interpreted as any factor that inhibit any protein or enzymes belonging to the same family as the HIF, "i.e. utilizing dioxygen (a cosubstrate), 2-oxoglutarate (2OG) (a cosubstrate) and Fe(II) (a cofactor). "Such enzymes are exemplified by phytanoyl coenzyme A hydroxylase, procollagen prolyl-r-hydroxylase, procollagen prolyl-3-hydroxylase, gamma-butyrobetaine hydroxylase, Alk B (a DNA repair enzyme) and other including predicted 2OG oxygenases identified on the basis of sequence analysis including a sub-family related to FIH (Hewitson et al. J BIOL CHEM 277 (29): 26351-26355, 2002)" according to the instant specification page 2, middle. Thus, instant FIH encompasses any protein, enzyme, or polypeptide that inhibits enzymes belonging to the same family as the HIF, including the PMI or CAS1 shown in the sequence alignment of Figure 2-A, page 26354, by the Hewitson et al. Therefore, the instant claims encompass a method

comparing any structure model derived from said genus factor inhibiting HIF family protein (FIH) with any chemical entity model structure having no structure limitation, wherein said structures are derived or obtainable by X-ray crystallography of a crystal comprising said FIH. The claimed method of using a genus of FIH structure described above cannot be adequately described by the disclosure of species of the structure coordinates in the Table 3. The species of instant case does not correlate structure and function from species to genus which have unlimited structure. Furthermore, the instant claims encompasses method of using a coordinate from X-ray diffraction of any FIH protein crystal. Because our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly understood, a method of the crystallization of a genus FIH encompassed by the breadth of the claims is not adequately described by the method of crystallization disclosed in the specification and the prior art. In general, for a species of crystallization to be adequately structurally described, the following must be adequately disclosed: a composition of the protein solution and a precipitant solution used in crystallization (exact concentrations, pH and volumes of all molecules used in the crystallization) must be described, including (1) the protein (preferably a SEQ ID NO of all included residues) (2) any ligand added (3) the precipitant solution). The species of crystallization noted in Example 2 of the instant specification have not adequately met this burden and the crystallization encompassed by the breadth of the claims is not described.

A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al*. Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). Therefore, the suitable condition disclosed in the specification to crystallize 16-314 of SEQ ID No. 1 cannot sufficiently describe a suitable condition of instant genus Claims.

15. Claims 1, 3-6 and 29-33 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method comprises using the structural coordinates of 1H2K, 1H2L, 1H2M and 1H2N (see Table 3) for a method of identifying, screening, characterizing or designing a chemical entity which binds to human Factor Inhibiting Hypoxia Inducible Factor (FIH, SEQ ID NO: undisclosed) identified as Q969Q7 (NCBI database), does not reasonably provide enablement for a method comprises using any structural model of any protein, enzyme, or polypeptide that inhibits enzymes belonging to the same family as the HIF including a X-ray diffraction measurements of a genus crystal comprising said FIH related protein.

The rejection was stated in the previous office action as it applied to previous Claims 1, 3-6 and 29-33. In response to this rejection, applicants have cancelled Claims 2 and 26; amended Claims 1 and 29 and traverse the rejection as it applies to the newly amended claims. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue and merely states that every points of the instant rejection are improper. Applicants argue that the Examiner's construction is overly broad because the present invention crystallized FIH, wherein the "FIH herein refer to FIH and homologues thereof" (see middle of page 17, Remarks). However, every protein(s) by the previous interpretation stated in office action is encompassed by the FIH homologues thereof; thus, the instant interpretation is proper.

Applicants argue that the statement of "typically, when crystallized, a FIH mutant will adopt a similar 3-dimensional structure to that adopted by the corresponding FIH" (see bottom of page 17, Remarks); thus, instant rejection is improper. However, as Applicants acknowledged, "when crystallized" the mutant have similar structure in certain time that is if the crystallization is successful. One skilled in the art would not be able to crystallize the full scope of protein in the instant method described in the specification. Applicant further argue that the specification "even mentions a limitation in the technique, that co-crystallization with CAD fragments shorter than twenty residues were not efficient". However, this is not a guidance to make and use the claimed method, but rather this is the evidence showing the preparation of the protein crystal is unpredictable. Just changing the length of ligand CAD with everything else is same including FIH makes one skilled in the art unable to form the FIH protein crystal.

Applicants argue the instant example is beyond the scope of the claims and argue that the structure coordinates identify that CAD binds to FIH, which is enough guidance to one skilled in the art to practice the claimed method. However, based on very widely varying genus claimed method and proper interpretation of FIH and

homolog thereof, the instant example does not provide adequate direction and/or guidance for claimed genus method. Also, the CAD was identified by the x-ray crystallography of co-crystal and was not identified by the method comprising comparison of the structural models *in silico*. If the instant examples were enough guidance, it should have forecasted the fact that CAD fragments shorter than twenty residues will not work for FIH co-crystal and the applicants should not have attempted to co-crystallize with CAD fragments shorter than twenty residues as shown on page 37, line 27 of instant specification. For the reasons stated above and the previous office action, the instant rejection is proper.

Claim Rejections - 35 USC § 102

19. Claims 1, 3, 5-6 and 29, 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Hewitson et al. (May 31, 2002, The Journal of Biological Chemistry, vol. 149, page 26351-26355).

The rejection was stated in the previous office action as it applied to previous Claims 1, 3-6 and 29-33. In response to this rejection, applicants have cancelled Claims 2 and 26; amended Claims 1 and 29 and traverse the rejection as it applies to the newly amended claims. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue the Hewitson reference is not 102(b) because it was not published more than one year prior to the priority date of the instant application.

The basis of 35 USC 102(b) is shown below.

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

As shown above, it is more than one year prior to the date of application for patent in the United States (emphasis added); and the foreign priority does not qualify for application for patent in the United States. Thus, instant rejection under 35 USC 102(b) is proper.

Applicants also argue the Examiner improperly interprets the instant FIH as including any 2 OG oxygenases identified on the basis of sequence analysis. Applicants argue that Hewitson does not disclose or suggest any crystal structure of FIH and does not disclose FIH structure coordinates.

As noted by Applicants, the specification adequately defines the term FIH as "References to FIH herein refer to FIH and homologues thereof" on page 4, line 25 of instant specification. Thus, although said definition of FIH is still unclear, the 2 OG oxygenases is encompassed by the FIH and/or homologues thereof; thus, the Examiner's interpretation is not overly broad and protein sequence relationship between 2OG oxygenases and FIH is directly from the instant specification page 2, middle, whereas the recitation is shown below.

As previously disclosed, the recited FIH is not clearly defined by the instant specification, the instant FIH has been interpreted as any “Factor Inhibiting HIF molecule”, not limited to, enzymes belonging to the same family as the HIF hydroxylases, i.e. utilizing dioxygen (a cosubstrate), 2-oxoglutarate (2OG) (a

cosubstrate) and Fe(II) (a cofactor). "Such enzymes are exemplified by phytanoyl coenzyme A hydroxylase, procollagen prolyl-r-hydroxylase, procollagen prolyl-3-hydroxylase, gamma-butyrobetaine hydroxylase, Alk B (a DNA repair enzyme) and other including predicted 2OG oxygenases identified on the basis of sequence analysis including a sub-family related to FIH (Hewitson et al. J BIOL CHEM 277 (29): 26351-26355, 2002)" according to the instant specification page 2, middle. Thus, the PMI or CAS1 shown in the sequence alignment of Figure 2-A, page 26354, by the Hewitson et al. is encompassed by a very broad FIH.

Hewitson et al. teach a method comprising comparing a structural model of phosphomannose isomerase (PMI) complexed with zinc, which are encompassed by the term FIH and a chemical entity, respectively, as shown in the three-dimensional structure in Figure 2-B, wherein the PMI three-dimensional structure meets the recited limitation of "structural model of FIH derived from structural factors or coordinates determined by X-ray diffraction" in Claims 1 and 29. The binding of Zn in the protein crystal structure of Hewitson et al. meets the limitations of Claims 4 and 31. The "identifying, screening, characterizing or designing a chemical entity which mimics or binds to FIH" is a preamble reciting an intended use, which does not contribute any structural limitations to the claimed method steps. The Hewitson et al. reference recites zinc(II) inhibits FIH (see middle of right column, page 26353) and in view of the assay using GST-HIF-1α-(775-826) as a substrate (see FIH Assays in bottom left column, page 26352), wherein the FIH of Hewitson et al. hydroxylate Asn803 of HIF (see title

and bottom right column, page 26351); thus, the zinc meets the limitations of Claims 5-6 and 32-33. Thus, the method of Hewitson et al. anticipates Claims 1, 4-6, 29, 31-33.

Claim Rejections - 35 USC § 103

16. Claims 3 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hewitson et al. (May 31, 2002, The Journal of Biological Chemistry, vol. 149, page 26351-26355) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). See MPEP §§ 2144 and 2144.04 regarding legal precedent as a source of rationale for rejection under 35 U.S.C. § 103.

Applicants argue the instant rejection fails the requirement set forth in Graham v. John Deere Co as shown on top of page 22, Remarks. Applicants argue that the Examiner has filed to satisfy the initial burden of establishing a prima facie case of obviousness. Applicants argue that the Exmainer's allegation that the structure coordinates are non-functional because they do not affect the performance of a computer are irrelevant; thus, improper. Applicants argue the Hewitson does not render the present claims obvious and does not teach or suggest any structural model of FIH.

However, as explained above, it is properly determined that the Hewitson et al. anticipate the scope of claimed invention. The only difference is the structure coordinate and the level of ordinary skill in the art for using any coordinate in the computer is rather simple, only if the coordinates are available. As noted in the previous office action, this particular data required by the instant claims is considered to be nonfunctional descriptive material. In *Gulack* and *Ngai*, the respective Courts held

that nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. According to *Gulack,* the key factor in analyzing the obviousness of the claims over the prior art is the determination that the machine-readable data comprising the structural coordinates of Table 3 is a known machine-readable medium and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. According to MPEP 2106.01, functional descriptive material consists of data structures and computer programs which impart functionality when employed as a computer component. (The definition of data structure is a physical or logical relationship among data elements, designed to support specific data manipulation functions and that "Nonfunctional descriptive material" includes but is not limited to music, literary works, and a compilation or mere arrangement of data. In this case, the data of Table 3 is an arrangement of data that represents a 3-D molecular structure. The data of Table 3 is not a data structure or a computer program that imparts functionality when employed as a computer component. The Appendix 3 structural coordinates are regarded as non-functional descriptive material and the claimed method is the same as the method of Hewitson et al. The data of Table 3, which are processed using a series of processing steps using a known algorithm, do not appear to impose a change in the processing steps or functioning of the computer and there is no evidence of record that the data of Table 3 imposes a change in the function of the computer. Put another way, the function of the computer

is the same whether the computer comprises the data of Table 3 or not. Thus, all claim limitations concerning the structure coordinate data of Table 3 are given no patentable weight as the data is considered to be non-functional descriptive material.

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the method as disclosed by Hewitson using any set of structural coordinates as defined in the claims with a reasonable expectation of success in view of the teachings of Hewitson et al. One would have been motivated to do this because Hewitson discloses the biological and structural implication "provide s a further target for the development of therapeutic agents that augment HIF activity in ischemia/hypoxic disease" (see bottom of left column, page 26354). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

17. Claims 1, 3-6 and 29-33 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652